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**Does Take-Home Naloxone Availability Increase Opioid Use?**

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JS: Through his university, JS is working with pharmaceutical industry to identify new or improved treatments and his employer (King's College London) has received grants, travel costs and/or consultancy payments; this includes investigation of new naloxone formulations and has included work with, past 3 years, Martindale, Indivior, Mundipharma (all of whom have naloxone products). His employer (King's College London) has also registered intellectual property on a novel buccal naloxone formulation, naming JS and colleagues, and he was earlier named in a patent registration by a pharmaceutical company regarding concentrated nasal naloxone spray. JS and colleagues have worked as consultants for the United Nations Office on Drugs and Crime (UNODC), supporting them with a project introducing take-home naloxone to four central and western Asian countries as well as contributing to local take-home naloxone schemes. For a fuller account, see JS's web-page at http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx

***Key statement:*** *Any potential increase in opiate use that might result from availability of take home naloxone is more than outweighed by its benefits in preventing overdose deaths.*

**What is the Concern?**

Administration of the opioid antagonist naloxone unquestionably saves lives and reduces organ damage by reversing respiratory depression from heroin/opioid overdose. The antidote is commonly available in emergency rooms and ambulances and has become standard equipment for many police officers and fire fighters. Broader public health efforts include take-home naloxone (THN) (1), i.e. pre-provision of an emergency naloxone supply to community members likely to experience or witness overdose, including people who use opioids (PWUO) and their close contacts. Multiple systematic reviews and studies have concluded that THN programs reduce opioid overdose mortality (2–7).

Nonetheless, lack of published data from randomized controlled trials makes THN prone to scepticism. Critics argue that overdose mortality is rising while THN expands (e.g. in the U.S. and Scotland (8,9)), because of 'Moral Hazard', i.e. by making opioids safer THN leads users to taking greater risks, such as consuming fentanyl (10). Doleac and Mukherjee claim that the evidence for THN is uncertain, citing a 14% mortality increase associated with broadened naloxone access (11). However, others have since highlighted methodological flaws (12) in Doleac and Mukherjee's analysis and have offered plausible alternative explanations for the rise in deaths, including changes in drug supply (e.g. fentanyl) (13).

This editorial asks whether there is any basis for the concern that THN availability increases opioid use and how we can frame this discussion to provide a reasoned understanding.

**The Need for a Balanced View**

As scientists, it is our duty to raise questions that allow for balanced examination of the available evidence: what unintended consequences of THN availability exist, and with what frequency and real-world implications do these occur? Analogies from other aspects of health and behaviour are manifold. For example, might people drive faster because their cars have seatbelts and/or an anti-lock braking system (ABS)? Might Epi-Pens encourage people with food allergies to make riskier (i.e. potentially allergenic) food choices?

A framework and *a priori* analytical approach would support a balanced examination. For an opioid overdose death to occur, at least two preceding steps exist – firstly, a pattern of drug use to produce the overdose, and secondly the absence or insufficiency of emergency resuscitative measures. Analyses of benefit from THN have focused on the latter (emergency resuscitation), but the former (overdose frequency and severity) also needs consideration.

A macro-level perspective is also required, with crucial assessment of the extent of behavior change and effect size at population level. The net effect of any public safety measure is a function of two variables, namely risk compensation and intervention effect. To illustrate, seat belts may encourage people to drive faster, but their effect in saving lives during accidents is so large that they are a net benefit for public health (14).

**Measuring Unintended Consequences of THN**

To date, only self-report data have been published, finding no overall increase in heroin use following THN receipt (15). Although these data are encouraging, a closer look reveals a more varied picture: while two-thirds (65%) of PWUO (n=325) reported unchanged or less frequent use, approximately one third (35%) increased use. But as with any self-report data, we need to assume potential limitations and biases (e.g. participants may have viewed it as socially desirable to report no increase in use). Moreover, for those already using heroin daily, the outcome measure (number of days using in past 30 days) was insensitive to increases in dose or frequency (i.e. greater than daily).

Objective data sources may offer more reliable observations. Can we incorporate smart devices to detect individual patterns of opioid use and changes in frequency or severity? Although such technological innovations are still being developed, existing databases may offer proxy outcomes. For example, ambulance call-outs (16) for overdoses within a predetermined timeframe post-THN receipt may indicate increased opioid use. However, ambulance calls are an important and expected aspect of THN distribution, administration, and aftercare. There is thus difficulty in distinguishing between intended and unintended consequences of THN.

A separate question concerns whether increased opioid use is truly an unintended outcome. Since dead people do not use drugs, and THN can prevent PWUO from dying, it has potential to increase population-wide opioid use *by design*. By analogy, public-access defibrillators increase the prevalence of heart attacks because some of those who otherwise (i.e. without defibrillation) would have died may go on to have future heart attacks.

Should policymakers make THN provision contingent upon its potential effects on opioid use? For the sake of argument, if broadened THN distribution increased opioid use in 10% of recipients, but the overall effectiveness of resuscitation across the whole population improved by 20%, then policymakers could decide that the overall situation is still one of major gain. If, on the other hand, 50% of THN recipients increased their use, while successful resuscitation rates only improved by 5%, then this is of concern.

Crucially, THN is one response of many in reducing overdose deaths, albeit an essential one. A recent study that modelled policy responses to address the U.S. opioid crisis noted that, among 11 interventions (including medication-assisted and psychosocial treatments, needle exchange services), naloxone availability would have the greatest effect on opioid-related deaths (with a 4% reduction), if considered alone (17). However, the authors concluded that a concerted effort rather than a single policy is required to substantially reduce deaths.

Although unintended consequences of THN provision cannot be ruled out (and future policy and practice should address these to the extent possible), greater harm could emerge from "reputational toxicity" (18) of the intervention. Myths around unintended consequences (based on anecdotal or unreliable evidence) can give THN a bad reputation, and such unfounded perception of risk could discourage providers from prescribing naloxone, which would reduce the net benefit of THN.

In summary, whilst there may be some individuals and circumstances in which THN availability could have unintended negative consequences, the cumulative effect remains a major benefit. Nevertheless, this should be quantified and studied without it being viewed as a betrayal of commitment to pursuing the benefits of THN or harm reduction.

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